UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,824	02/13/2002	Esin F. Kosal	P50785C1	8083

7590 06/02/2003

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939

EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	7

DATE MAILED: 06/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/074,824	Applicant(s) KOSAL ET AL.	
	Examiner Thomas McKenzi,e Ph.D.	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. This action is in response to an application filed on 2/13/02. There are sixteen claims pending and sixteen under consideration. Claims 1-16 are method of synthesis. This is the first action on the merits. The application concerns a process of preparing the sodium salt of the antibiotic amoxycillin.

Abstract

2. Applicant is reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. For processes, the type reaction, reagents, and process conditions should be stated, generally illustrated by a single example unless variations are necessary. The abstract is too short and generic. Examiner suggests claim 1, including the figure, and the utility.

Priority

3. The current status of all nonprovisional parent applications referenced should be included. The parent application has become abandoned.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Ortega ('585, Ref AA). According to the MPEP §2113 "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964." Thus, claim 16 reads on any crystalline alkali metal salt of amoxycillin. The compound sodium amoxycillin is found in lines 1-5, column 2 of the reference. Sodium is an alkali metal. The teaching in the reference regarding the crystalline nature of the compound is discussed below.

5. Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Callander ('958, Ref AB). Crystalline alkali metal salts of amoxycillin are found in lines 45-51, column 1 of the reference.

6. Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Corsi (EP 596,262 A1, Ref BA). Crystalline sodium amoxycillin is found in lines 32-35, page 6 of the reference.

7. Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Cabre (WO 97/15579 A1, Ref BB). Crystalline sodium amoxycillin is found in the title and abstract of the reference.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ortega ('585, Ref AA). In the passage spanning line 24, column 1 to line 4, column 4. See also claims 1-5 of the reference. The reference teaches the process of preparing the sodium salt of the antibiotic amoxycillin by preparing an amine salt of amoxycillin *in situ* in a two-solvent mixture. That process is taught generically in lines 40-52, column 1. The salifying agent sodium diethyloxalacetate is taught in line 26, column 1. The solvents are taught in lines 46-52, column 1. Isolation of sodium salt of the antibiotic amoxycillin by precipitation and filtration is taught in lines 2-3, column 2. The reference is silent as to the crystalline nature of the product formed. However, the word "precipitation" and act of isolation by filtration is understood in the organic chemical arts that the solid formed is

crystalline and not colloidal. The contrast made in line 4, column 2 of the reference over lyophilization, which produces non-crystalline, glassy material, is noted.

The Applicants claim a process of forming a suspension of an amine salt in one solvent, adding a second solvent to form a homogeneous solution, adding a salifying agent, and isolating the crystalline product. The difference between the claimed and taught processes is the manner in which the amine salt solution is formed in the two-solvent mixture. In Applicants' claims, the second polar solvent is added second after the amine salt is formed, in the reference the second polar solvent is added before the amine salt is formed. Applicants' process is obvious over that taught in the reference because changing the order of steps in a known multi-step process does not make the process unobvious when no unexpected results occur, *Ex parte Rubin,* 128 USPQ 440, *Cohn et al v. Comr. Pats*. 148 USPQ 486. Thus, claims 1, 2, 6, and 9 are made obvious.

Applicants' claims 3, 7, and 8 add the limitations of specific amine salts and methanol as the polar solvent. Those limitations are found in the reference in 43-44, column 1 and line 51, column 1 respectively. Thus, claims 3, 7, and 8 are also made obvious.

9. Applicants' claims 4 and 5 require that the first solvent be methyl acetate. The reference teaches that the solvent can be acetonitrile, methylene chloride, or 1,2-dichloroethane in lines 46-52, column 1. The difference between Applicants' claims and the teachings of the reference is the solvent employed. No more than routine skill is required for the process chemist to optimize the solvent choice. To quote the Board of Patent Appeals and Interferences *Ex parte Goldschmidt*, 123 USPQ 41 "It is our opinion that it does not amount to invention for the skilled chemist ... to determine ... which specific organic solvent is most suitable". To quote Judge Gajarsa of the U.S. Court of Appeals Federal Circuit in *Eli Lilly & Co. v. Barr Laboratories Inc.* 55 USPQ2d 1609 at 1613, "choosing a suitable recrystallization solvent was well known to one of ordinary skill in the art. In particular, Dr. Elias J. Corey ("Corey"), a Nobel laureate, testified that fluoxetine hydrochloride is "generally quite easy to purify by recrystallization". Corey also explained that, although it requires some experimentation, selecting a recrystallization solvent is "very straightforward". Further, Barr's expert testified that "in 1974, sometimes the recrystallization of amine hydrochlorides was indeed routine"." In the alternative, the claimed methanol solvent is an obvious homologue of the taught ethanol solvent. Thus, claims 4 and 5 are also made obvious.

10. Claims 1-14 are rejected under 35 U.S.C. 103(a) as obvious over Callander ('958, Ref. AB). The reference teaches the process of preparing the sodium salt of the antibiotic amoxycillin by preparing the diethyl amine salt of amoxycillin *in situ* in a two-solvent mixture. That process is taught specifically in the passage spanning line 44, column 2 to line 21, column 3. The salifying agent sodium 2-ethylhexanoate is taught in line 51, column 2. The alcohol solvents are taught as isopropanol and ethanol in lines 46 and 66, column 2 respectively. Isolation of sodium salt of the antibiotic amoxycillin by precipitation and filtration is taught in lines 54-55, column 2. The reference describes the product as crystalline in line 46, column 1, line 56, column 1, and line 24, column 2. The Applicant claims a process of forming a suspension of an amine salt in one solvent, adding a second solvent to form a homogeneous solution, adding a salifying agent, and isolating the crystalline product. The difference between the claimed and taught processes is the manner in which the amine salt solution is formed in the two-solvent mixture. In Applicants' claims, the second polar solvent is added second after the amine salt is formed, in the reference the second polar solvent is added before the amine salt is formed. Applicants' process is obvious over that taught in the reference because changing the order of steps in a known multi-step process does not make the process unobvious when no unexpected results occur, *Ex parte Rubin,* 128 USPQ

440, *Cohn et al v. Comr. Pats.* 148 USPQ 486. Thus, claims 1-3, 6, 7, and 9 are made obvious.

Applicants' claim 10 requires the salifying agent be a sodium salt of an (C1-5) alcohol. Sodium methoxide as such a reagent is taught in lines 3-4, column 2. Thus, claim 10 is also made obvious. Applicants' claim 12 requires the salifying agent to be added in solution. Line 53, column 2 teaches methyl isobutyl ketone to make such a solution. Thus, claim 12 is made obvious.

11. Applicant's claims 4 and 5 require the polar solvent to be methyl acetate. Applicants' claims 8 and 11 require that the second alcohol solvent be methanol. The reference teaches amide solvents for the first solvent in lines 58-63, column 1. The teaching of isopropanol and ethanol for the second alcohol solvent were discussed above. The difference between Applicants' claims and the teachings of the reference are the solvents employed. No more than routine skill is required for the process chemist to optimize the solvent choice. To quote the Board of Patent Appeals and Interferences *Ex parte Goldschmidt*, 123 USPQ 41 "It is our opinion that it does not amount to invention for the skilled chemist ... to determine ... which specific organic solvent is most suitable". To quote Judge Gajarsa of the U.S. Court of Appeals Federal Circuit in *Eli Lilly & Co. v. Barr Laboratories Inc.* 55 USPQ2d 1609 at 1613, "choosing a suitable recrystallization solvent was well

known to one of ordinary skill in the art. In particular, Dr. Elias J. Corey ("Corey"), a Nobel laureate, testified that fluoxetine hydrochloride is "generally quite easy to purify by recrystallization". Corey also explained that, although it requires some experimentation, selecting a recrystallization solvent is "very straightforward". Further, Barr's expert testified that "in 1974, sometimes the recrystallization of amine hydrochlorides was indeed routine"." In the alternative, the claimed methanol solvent is an obvious homologue of the taught ethanol solvent. Thus, claims 4, 5, 8, and 11 are made obvious.

12. Applicants' claims 13 and 14 require the salifying agent be added in methanol and ethyl acetate solution. Line 53, column 2 teaches a methyl isobutyl ketone solution of the salifying agent. The difference between the claims and taught process is the solvent used to make this solution. The reasoning is as above and claims 13-14 are made obvious.

13. Claims 1-9, 11, 12, and 15 are rejected under 35 U.S.C. 103(a) as obvious over Corsi (EP 596,262 A1, Ref BA). The reference teaches the process of preparing the sodium salt of the antibiotic amoxycillin by preparing a salt of amoxycillin with "a suitable base" *in situ* in a two-solvent mixture. That process is taught generically in the passage spanning line 34, page 2 to line 7, page 3. The salifying agent sodium 2-ethylhexanoate is taught in line 45, page 2. The base

triethyl amine is taught in line 44, page 2. The two solvents are taught as methanol and C_2-C_5 alcohols in line 36, page 2. Isolation of sodium salt of the antibiotic amoxycillin by precipitation and filtration is taught in lines 6-7, column 7. The reference describes the product as "crystals" in line 32, page 6. The Applicants claim a process of forming a suspension of an amine salt in one solvent, adding a second solvent to form a homogeneous solution, adding a salifying agent, and isolating the crystalline product. The difference between the claimed and taught processes is the manner in which the amine salt solution is formed in the two-solvent mixture. In Applicants' claims, the second polar solvent is added second after the amine salt is formed, in the reference the second polar solvent is added before the amine salt is formed. Applicants' process is obvious over that taught in the reference because changing the order of steps in a known multi-step process does not make the process unobvious when no unexpected results occur, *Ex parte Rubin,* 128 USPQ 440, *Cohn et al v. Comr. Pats.* 148 USPQ 486. Thus, claims 1-3, 6-9, and 11 are made obvious.

Applicants claim 12 requires the salifying agent be added in solution. Line 36-37, page 2 teaches methyl acetate to make such a solution. Applicants' claim 15 requires reverse addition of the amine salt to the solution of the salifying agent.

That is taught in lines 25-26, page 3 and lines 30-31, page 6. Thus, claims 12 and 15 are made obvious.

14. Applicants' claims 4 and 5 require that the first solvent be methyl acetate. The reference teaches that the solvent is a C_2-C_5 alcohol in line 36, page 2. The difference between Applicants' claims and the teachings of the reference is the solvent employed. No more than routine skill is required for the process chemist to optimize the solvent choice for reasons cited above.

15. Claims 1-15 are rejected under 35 U.S.C. 103(a) as obvious over Cabre (WO 97/15579 A1, Ref BB). The reference teaches the process of preparing a crystalline sodium salt of the antibiotic amoxycillin by preparing a salt of amoxycillin with "a suitable amine" *in situ* in ethanol solution. That process is taught generically in the lines 7-17, page 2. The salifying agents are taught in lines 3-8, page 4 including methoxide, ethoxide, and the C-5 carboxylic acid pivalate. Sodium 2-ethylhexanoate is taught in line 1, page 6. The bases triethylamine, diethyl amine, and diisopropylamine are taught in lines 23-25, page 2. The solvent is taught as ethanol in line 4, page 2. Isolation of sodium salt of the antibiotic amoxycillin by filtration is taught in the last line, page 4. The reference describes the product as "crystals" in the same passage. The Applicants claim a process of forming a suspension of an amine salt in one solvent, adding a second solvent to

form a homogeneous solution, adding a salifying agent, and isolating the crystalline product. The difference between the claimed and taught processes is Applicants requirement that the process occur in a two-solvent mixture. The teaching to add a second solvent methyl acetate is found in the reference in line 17, page 2. Thus, Applicants' claims 1-7, 9, and 10 are anticipated.

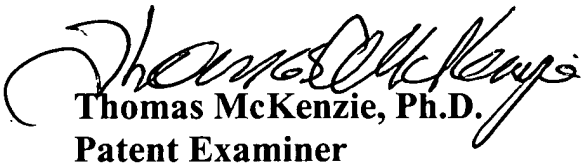
Applicants' claim 8 requires that the alcohol solvent be methanol. Claim 11 adds the limitation that the salifying agent be sodium 2-ethylhexanoate. The teaching of the salsifying agent in the reference was discussed above. The difference between Applicants' claims and the teachings of the reference are the use of methanol rather than ethanol as taught in the reference. No more than routine skill is required for the process chemist to optimize the solvent choice for reasons cited above. In the alternative, the claimed methanol solvent is an obvious homologue of the taught ethanol solvent. Thus, claims 8, and 11 are made obvious.

Applicants claim 12 requires the salifying agent be added in solution. Lines 1-2, page 4 of the reference teach ethanol. Applicants' claim 15 requires reverse addition of the amine salt to the solution of the salifying agent. That is taught in line 2, page 6. Thus, claims 12 and 15 are made obvious.

16. Applicants' claims 13 and 14 require the salifying agent be added in methanol and ethyl acetate solution. Line 1, page 6 teaches an ethanol solution. The difference between the claims and taught process is the solvent used to make this salsifying solution. No more than routine skill is required for the process chemist to optimize the solvent choice for reasons cited above. Thus, claims 13 and 14 are made obvious.

Conclusion

17. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.



Thomas McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK
May 30, 2003